REMARKS

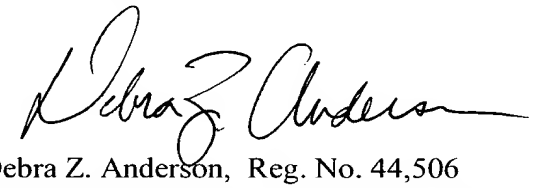
Rejections under 35 USC §103

Claims 23 and 51-61 were rejected under 35 USC §103 as unpatentable over the Kim and Peacock reference in view of the Brunschwig et al. reference. Applicant respectfully traverses this rejection as it may pertain to the amended claims.

As amended, Claim 23 is directed to a cell having a lipidated protein incorporated into the cell membrane, and a fusion protein bound thereto. The fusion protein comprises a first and second domain, the second domain having a *trans* signaling and/or adhesion function. It is submitted that the cited references do not show a fusion protein having these functions attached via a lipidated protein. It is further submitted that it would not be obvious to combine these references, as has the Examiner, to arrive at the present invention, for the reasons previously submitted in the Declaration of Mark Tykocinski, filed in the parent case, now US Patent 6316256. A copy of this declaration is enclosed for your convenience. Applicant respectfully submits that Claim 23, and the claims depending therefrom, Claims 51-61, are not obvious and requests withdrawal of this rejection.

As all outstanding issues have been addressed, Applicant respectfully submits Claims 23 and 51-61 are in condition for allowance; such action is respectfully requested at an early date.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	Group Art Unit 1642
MARK L. TYKOCINSKI ET AL.	Examiner Alana M. Harris, Ph.D.
Serial No. 09/476,828	Attorney Docket No. 285332-00002
Filed January 3, 2000	
METHODS FOR PROTEIN TRANSFER	

DECLARATION OF MARK L. TYKOCINSKI

I, Mark L. Tykocinski, being duly sworn hereby declare as follows:

1. I have a B.A. Degree in Biology from Yale University, awarded in 1974, and an M.D. from New York University, awarded in 1978.

2. From 1978 to 1979, I was a resident in the Department of Internal Medicine at Columbia-Presbyterian Medical Center (New York, NY); from 1979 to 1981 I was an Anatomic Pathology resident in the Department of Pathology at New York University (New York, NY); and from 1981 to 1983 I was a Medical Staff Fellow in the Laboratory of Immunogenics, National Institute of Allergy and Infectious Diseases, National Institutes of Health (Bethesda, MD);

3. From 1983 to present, I have held various faculty appointments as listed in Exhibit A, most recently as Simon Flexner Professor and Chair (with tenure), Department of Pathology and Laboratory Medicine, University of Pennsylvania (Philadelphia, PA).

4. I am a member in the professional societies listed in Exhibit B.

5. I have received the awards and honors listed in Exhibit C.

6. I am an author of the publications listed in Exhibit D.

7. My various professional activities, including teaching responsibilities, academic committees, executive training programs, seminars and invited lectureships, national and international presentations, editorial positions, organizing roles in scientific meetings, advisory boards and patents are listed in Exhibit E.

8. I am a named inventor on two patents and six patent applications and have an inventor's understanding of the patent system.

9. I am a named inventor on the captioned application. I participated in the preparation of the patent application, and carefully reviewed the application prior to its filing. I have read the previous Office Action issued in this case, and participated in the response to that Office Action. I have read the outstanding Office Action, and have participated in the response to that Office Action, including responding to the rejection made under 35 U.S.C. § 112, second paragraph and the rejection made under 35 U.S.C. § 103.

10. It is my well considered opinion that Claims 1-22 would not be considered indefinite by those skilled in the art, in view of the specification and examples provided therein. Additionally, there are numerous assays and procedures, well-known in the art, for assessing the immunoregulatory function of a protein or peptide, or fragment or derivative thereof. These assays are routine, simple-to-perform, and in many cases, available (such as ELISA) in the form of commercial kits to carry them out, and are widely advertised in any one of a number of immunology journals. Examples of such assays include: 1) monitoring ^{3}H-thymidine incorporation, as a measure of cellular proliferation (for example, T cell proliferation); 2) monitoring the lysis of ^{51}Cr-labeled target cells, as a measure of antigen-specific cytolytic activity (for example, for cytotoxic T cells); 3) performing the JAM assay, as another measure of antigen-specific cytolytic activity; and 4) measuring changes in the secretion of pro-inflammatory and other cytokines, as a measure of immune cell activation (for example, dendritic cell or T cell activation).

11. The above-listed assays are only a few of many assays known and widely used in the art. These various assays can be used to determine whether a candidate protein or peptide, or a fragment or derivative thereof, either increases or decreases particular immune responses. It is my well considered opinion, therefore, that one skilled in the art would easily be able to determine which protein or peptide fragments or derivatives would elicit the desired immune response and that Claims 1-22 are not indefinite.

12. It is my well considered opinion that the invention embodied in Claims 1-13, 15 and 18-21 would not be obvious to one skilled in the art, in view of the references cited. Kim and Peacock disclose a method of antibody transfer using chemically lipidated protein A; Brunschwig discloses a method of transferring various proteins using GPI to attach proteins to the cell surface. Significantly, the GPI moieties are attached to the proteins by the cell's natural synthetic machinery. These references cannot be combined to arrive at the present invention.

13. Even with knowledge of costimulator-GPI protein transfer, as described in Brunschwig et al., one skilled in the art would not be motivated to combine this

method with the non-GPI antibody transfer method of Kim and Peacock. Among the reasons for this are the following:

i) GPI proteins were known to segregate into cholesterol-rich membrane microdomains, but this was not known to be the case for palmitated protein A. This is quite significant, since it is generally believed that activation of T cells by antigen-presenting cells requires clustering of *trans* signaling molecules into microdomains, which in turn aggregate at the critical antigen-presenting cell:T cell contact sites. See, for example, Moran, M., and Miceli, M.C., *"Engagement of GPI-linked CD48 contributes to TCR signals and cytoskeletal reorganization: a role for lipid rafts in T cell activation"*, Immunity 9:787, 1998, in which the ability of GPI proteins to migrate to microdomains and lipid rafts in the cell membrane is described, and which provides further evidence that surface localization of GPI proteins on both the T cell and APC sides is important in T cell activation. Whereas costimulator-GPI fusion proteins would be expected to segregate into specialized *trans* signaling units in this way, there is no compelling reason to believe *a priori* that costimulator-Fc:palmitated protein A conjugates would similarly do so. The high degree to which GPI fusion proteins are integrated into these surface microdomains is highlighted by the fact that once positioned in these membrane structures, they can even signal in *cis* through their anchoring GPI lipids; palmitated protein A would simply not be able to do this. GPI fusion proteins achieve a topological distribution on the surface membrane that would not necessarily be expected of other membrane-anchoring, even lipidated, proteins.

ii) Whereas costimulator-GPIs are, by definition, a single molecular moiety, the costimulator-Fc:palmitated protein A conjugates of the present invention are comprised of two distinct units. Since the component units of the latter conjugates are each quite large, one would expect these conjugates to project away from the cell surface a considerable distance, and certainly substantially further than costimulator-GPIs project from the cell surface. This complication would dissuade one from turning to costimulator-Fc:palmitated protein A conjugates, with the expectation of topological distortion at the intercellular *trans* signaling interface. Also relevant is the fact that protein A is inherently pentavalent, which would further add to the sheer bulk of the *trans* signaling unit and potentially interfere with its achieving physical proximity with the antigen signaling unit.

iii) The immunoglobulin:palmitated protein A conjugates delivered according to the Kim and Peacock method, as described in their publication, turn out to be relatively short-lived at the cell surface. Hence, one would have been dissuaded from abandoning GPI proteins in favor of short-lived palmitated proteins. As part of the present

invention, the Kim and Peacock procedure was modified by increasing the temperature from 4°C to 37°C; at this higher temperature enhanced membrane stability was achieved.

14. It is my well considered opinion that one skilled in the art could not have predicted that the use of palmitated or otherwise lipidated fusion proteins or peptides, or fragments or derivatives thereof, would retain their *trans* signaling capability, based on the teachings of the references, or on any other teachings.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4127101
Date

Mark L. Tykocinski

EXHIBIT A

FACULTY, HOSPITAL AND ADMINISTRATIVE APPOINTMENTS

Faculty Appointments:

1983-90	Assistant Professor, Department of Pathology, Case Western Reserve University (Cleveland, OH)
1987-90	Assistant Professor of Oncology, (secondary appointment), Case Western Reserve University
1990-95	Associate Professor (with tenure), Department of Pathology, Case Western Reserve University
1990-96	Associate Professor Oncology, (secondary appointment), Case Western Reserve University
1995-98	Professor (with tenure), Department of Pathology, Case Western Reserve University
1995-98	Professor of Oncology (secondary appointment), Case Western Reserve University
1998 -	Adjunct Professor, Department of Pathology, Case Western Reserve University
1998 -	Simon Flexner Professor and Chair (with tenure), Department of Pathology and Laboratory Medicine, University of Pennsylvania (Philadelphia, PA)

Hospital and Administrative Appointments:

1983-98	Staff Physician, University Hospitals of Cleveland
1985-91	Participating Physician and Pathology Specialist MetLife HealthCare Network of Ohio, Inc.
1993-98	Director (and Founder), Gene Therapy Program, CWRU Cancer Center
1994-98	Director (and Founder), Gene Therapy Facility, CWRU School of Medicine
1994-98	Director, Molecular Biology Core Facility, Skin Disease Research Center, CWRU
1995-97	Co-Principal Investigator, Phase I clinical trial for gene therapy/immunotherapy of human glioblastoma
1998 -	Chair, Department of Pathology and Laboratory Medicine, University of Pennsylvania
1999 -	Staff Physician, Hospital of the University of Pennsylvania (Philadelphia, PA)
1999 -	Staff Physician, Presbyterian Medical Center (Philadelphia, PA)
1999 -	Staff Physician, Pennsylvania Hospital

	(Philadelphia, PA)
1999 -	Participating Physician and Pathologist, Preferred Health Network (Multi-State)
2000 -	Clinical Effectiveness and Quality Subcommittee—Laboratory Leader, University of Pennsylvania Medical Center (Philadelphia, PA)
2000-	Advisory Committee, Program of Excellence in Gene Therapy at the University of Pennsylvania (Philadelphia, PA)
2000-	Graduate Group in Immunology, University of Pennsylvania Health System (Philadelphia, PA)
2000-	Universities Associated for Research and Education in Pathology, UAREP Board of Directors

EXHIBIT B

MEMBERSHIP - PROFESSIONAL SOCIETIES AND COMMITTEES

National Societies:

1984 -	American Society for Investigative Pathology
1985 -	American Association for Cancer Research
1985 -	International Society of Differentiation
1985 -	National Institutes of Health Alumni Assoc.
1991 -	American Association of Immunologists
1991 -	Marine Biological Laboratory, Member
1998 -	Association of Pathology Chairs
2000 -	American Association of University Pathologists

Local Societies:

1989-98	Cleveland Medical Library Association
1999 -	Pennsylvania Association of Pathologists
1999 -	Pennsylvania Medical Society

National Scientific Committees:

Member, American Association of Pathologists Ad Hoc Committee on Initiatives in Education, 1990

Visiting Scholar in Biotechnology, Ohio Academy of Science, 1990

Ad Hoc Member, NIH Pathology B Study Section, 1990

Member, NIH Pathology B Study Section, 1991-1996 (Chairman 1994-96)

Ad Hoc Member, NIH Pathology B AHR M1 study section, 1992

Ad Hoc grant reviewer for the American Heart Association, 1992

Ad Hoc grant reviewer for the Israel Science Foundation, 1993

Ad Hoc Member, NIH Pathology B AHR M2 Study Section, 1993

Member, Research Services Committee, Marine Biological Laboratory, 1995-96

Member, Neoplasia Subsection of the American Society for Investigative Pathology, 1995

Member, Experimental Therapeutics Subcommittee Section on Gene Therapy of the American Association of Cancer Research, 1995

Ad Hoc Member, NIH Experimental Therapeutics 2 Special Emphasis Panel, 1995

External Reviewer, Kennedy Institute of Rheumatology for the Arthritis and Rheumatism Council, Chesterfield, Derbyshire, England, 1996

Member, 1996 Program Committee, American Assoc. for Cancer Research, 1996

Chair, NIH Biological and Physiological Science Special Emphasis Panel, ZRGZ, NEP (2), 1996
Ad Hoc Member, NIH Pathology B Study Section, 1997
Chair, NIH Experimental Therapeutics Special Emphasis Panel, 1997
Ad Hoc Reviewer, New York University 1997 Whitehead Fellowships for Junior Faculty in Biological Sciences, 1997
Member, NIH Site Visit Team, Tulane Regional Primate Research Center, 1997
Ad Hoc Member, NIH Fellowship Review Committee SSS-1, 1998
Chair, NIH Fellowship Review Committee SSS-1, 1998
Chair, NIH Biological and Physiological Sciences Special Emphasis Panel, ZRG2 SSS-1 (1), 1998

Local Scientific Committees:

Member, CWRU Cancer Center Grant Review Committee, 1986-90
Member, Molecular Biology Program, CWRU Cancer Center, 1986-98
Chairman, Diagnostic Molecular Biology and Planning Search Committee, Institute of Pathology, CWRU, 1988-89
Member, Planning Committee for AIDS Program Project, 1988-90
Member, Hematopoietic Cell Program, CWRU Cancer Center, 1988-90
Member, CWRU Recombinant DNA Experimentation Review Board, 1988
Faculty Member, Cell Biology Program, CWRU, 1989-98
Research Committee liaison to the Dean's Musculoskeletal Task Force, CWRU, 1990-91
Ad Hoc Member, Oncology Task Force, CWRU Cancer Center, 1990
Member, Molecular Virology and AIDS Program, CWRU Cancer Center, 1991-98
Member, Hematopoietic and Immune Cell Biology Program, CWRU Cancer Center, 1991-98
Faculty Member, Cell and Molecular Biology Training Program, CWRU, 1992-98
Faculty Member, Pharmacological Sciences Training Program, CWRU, 1992-98
Member, Brain Tumor Research Working Committee, CWRU, 1993
Faculty Member, Graduate Program in Molecular Virology, CWRU, 1993-98
Faculty Member, Research Oncology Training Grant, CWRU, 1993-98
Faculty Member, Immunology Training Grant, CWRU, 1995-98

Member and Chair, Gene Therapy Facility Advisory Committee, CWRU, 1997-98

Member, ACS Institutional Grant Review Committee, CWRU, 1997

EXHIBIT C

AWARDS AND HONORS

1993	Guest Professor, Fourth Military Medical University, Shanghai, China
	Guest Professor, Second Military Medical University, Xi'an, China
1994-96	Chairman, NIH Pathology B Study Section
1995	Warner-Lambert/Parke-Davis Award
	(American Society for Investigative Pathology, FASEB)
2001-	Member, Pluto Society – American Association of University Pathologists

EXHIBIT D

PUBLICATIONS

1. Lown, B., **Tykocinski, M.,** Garfein, A., and Brooks. Sleep and ventricular premature beats. Circulation 48:691-701, 1973.

2. Wilkinson, J.M., **Tykocinski, M.L.,** Coligan, J.E., Kimball, E.S., and Kindt, T.J. Rabbit MHC antigens: occurrence of non-beta-2-microglobulin associated class I molecules. Mol. Immunol. 19:1441-1451, 1982.

3. **Tykocinski, M.,** Schinella, R.A., and Greco, M.A. Fibroblastic reticulum cells in human lymph nodes: an ultrastructural study. Arch. Path. 107:418-422, 1983.

4. **Tykocinski, M.,** Schinella, R.A., and Greco, M.A. The pleomorphic cells of advanced disseminated mycosis fungoides: an ultrastructural study. Arch. Path. 108:387-391, 1984.

5. **Tykocinski, M.L.** and Max, E.E. CG dinucleotide clusters in MHC genes and in 5' demethylated genes. Nucl. Acids Res., 12:4385-4396, 1984.

6. **Tykocinski, M.L.,** Marche, P.N., Max, E.E., and Kindt, T.J. Rabbit class I MHC genes: cDNA clones define full-length transcripts of an expressed gene and a putative pseudogene. J. Immunol. 133:2261-2269, 1984.

7. Marche, P.N., **Tykocinski, M.L.,** Max, E.E., and Kindt, T.J. Structure of a functional rabbit class I MHC gene: similarity to human class I genes. Immunogenetics 21:72-82, 1985.

8. Rabson, A.B., Hamagishi, Y., Steele, P.E., **Tykocinski, M.L.,** and Martin, M.A. Characterization of human endogenous retroviral envelope RNA transcripts. J. Virol. 56:176-182, 1985.

9. Medof, M.E., Lublin, D.M., Holers, V.M., Ayers, D.J., Getty, R.R., Leykam, J.F., Atkinson, J.P., and **Tykocinski, M.L.** Cloning and characterization of cDNAs encoding the complete sequence of decay-accelerating factor of human complement. Proc. Natl. Acad. Sci. (USA) 84:2007-2011, 1987.

10. Werber, H.I., Emancipator, S.N., **Tykocinski, M.L.,** and Sedor, J.R.: The interleukin I gene is expressed by rat glomerular mesangial cells and is enriched in immune complex glomerulonephritis. J. Immunol. 138:3207-3212, 1987.

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13. Cheung, N.-K., Walter, E., Smith-Mensah, W.H., Ratnoff, W., **Tykocinski, M.L.,** and Medof, M.E. Decay accelerating factor (DAF) protects human tumor cells from complement mediated cytotoxicity in vitro. J. Clin. Invest. 81:1122-1128, 1988.

14. Hambor, J.E., Hauer, C.A., Shu, H.-K., Groger, R.K., Kaplan, D.R., and **Tykocinski, M.L.** Use of an Epstein-Barr virus episomal replicon for anti-sense RNA-mediated gene inhibition in a human cytotoxic T cell clone. Proc. Natl. Acad. Sci. (USA) 85:4010-4014, 1988.

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49. Weber, M. and **Tykocinski, M.L.** Antisense modulation of the ICAM-1 phenotype of a model human bone marrow stromal cell line. Exp. Cell Res., 244:239-248, 1998.

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54. Rachmilewitz, J., Riely, and **Tykocinski, M.L.** Placental protein 14 functions as a direct T-cell inhibitor, Cell. Immunol.191:26-33, 1999.

55. Kopf, E., Bibi, O., Ayesh, S., Ariel, J., Schulze, E., Schneider, T., **Tykocinski, M.L.** Erdmann, V., Laster, M., Holthuizen, E., de Groot, N., and Hochberg, A. The in vivo and in vitro expression of H19 and IGF-2 genes in human bladder carcinoma cell lines.

56. Tanos, V., Prus, D., Weinstein, D., **Tykocinski, M.L.**, de-Groot, N., Hochberg, A., Ariel, I. Expression of the imprinted H19 oncofetal RNA in epithelial ovarian cancer. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 85: 7-11, 1999.

57. Fayen, J. D., and **Tykocinski, M. L.** The expansion of human gamma-delta T cells in response to Daudi cells requires the participation of CD4+ T cells. Immunology, 97: 272-279, 1999.

58. Brunschwig, E.B., Fayen, J.D., Medof, M.E., and **Tykocinski, M. L.** Protein transfer of glycosyl-phosphatidylinositol (GPI)-modified murine B7-1 and B7-2 costimulators. J. Immunother, 22: 390-400, 1999.

59. Ohana, P., Kopf, E., Bibi, O., Ayesg, S., Schneider, T., Laster, M., **Tykocinski, M. L.**, de Groot, N., Hochberg, A. The Expression of the H19 Gene and its Function in Human Bladder Carcinoma Cell Lines. FEBS Letters. 454: 81-4, 1999.

60. Chen, A., Zheng, G., and **Tykocinski, M.L.** Hierarchical Costimulator Thresholds for Distinct Immune Responses: Application of a Novel two-step Fc Fusion protein transfer method. Journal of Immunology, 164: 705-711, 2000.

61. Geho, David H., Fayen, John D., Jackman, Robin M., Moody, Branch D., Porcelli, Steven A., and **Tykocinski, M. L.** Glycosyl-Phosphastidylinositol Reanchoring Unmasks

Distinct Antigen-Presenting Pathways for CD1b and CD1c. *Journal of Immunology,* 165: 1272-1277, 2000.

62. Riley, G., J. Rachmilewitz, P. Koo, and **M. L. Tykocinski.** α2-Macroglobulin modulates the immunoregulatory function of the lipocalin placental protein 14. *Biochem. J.*, 351: 503-508, 2000.

63. Jui-Han Huang and **M. L. Tykocinski.** CTLA-4-Fas ligand functions as a *trans* signal converter protein in bridging antigen-presenting cells and T cells. *International Immunology.* 13, No. 4: 529-539, 2001.

64. Jui-Han Huang and **M. L. Tykocinski**. CTLA-4-Fas ligand Functions as a Trans Signal Converter Protein in Bridging Antigen-Presenting Cells and T Cells. *International Immunology* 13: 529-539, 2001.

65. Premkumar, Daniel R. D., Y. Fukuoka, D. Sevlever, E. Brunschwig, T. R. Rosenberry, **M. L. Tykocinski,** and E. Medof. Properties of Exogenously Added GPI-Anchored Proteins Following Their Incorporation Into Cells. Journal of Cellular Biochemistry, 2001.

66. Xiong, N., Mao, J., Chakraborty, S., Eshleman, S., and **Tykocinski, M.L.** Effects of N-glycosylation on secretion and immunosuppressive function of placental protein 14 (glycodelin). Submitted, 2001.

67. Mao, J., Geho, D., Chakraborty, S., Feng, Y., Anderson, V., Shoham, M., and **Tykocinski, M.L.** Retinoid binding potential of two placental protein 14 variants. Submitted, 2001.

68. Rachmilewitz, J. and **Tykocinski, M.L.** T cell activation threshold is elevated by an immunoregulatory lipocalin. Submitted, 2001.

69. Weber, M.C., Ziats, N.P., Chen, A., Ratnoff, O.D., **Tykocinski, M.L.**, Riely, G. Inhibition of Factor XII (Hageman Factor) Activation by the Immunosuppressive Protein PP14. In preparation, 1999.

70. Xiong, N., Mao, J., Feng, Y., Chakraborty, S., and **Tykocinski, M.L.** Secretory properties of two placental protein 14 variants. In preparation, 2001.

71. Xiong, N., Weber, M., and **Tykocinski, M.** Placental protein 14 (glycodelin) is secreted from activated platelets. In preparation, 2001.

72. Chen, A., Fayen, J., Trefzer, U., Brunschwig, E., and **Tykocinski, M.L.** Poly-histidine tagged glycosyl-phosphatidylinositol-modified human B7-1 retains costimulator function. In preparation, 2001.

73. Riely, G., Koo, P. Chakraborty, S. and **Tykocinski, M.L.** Placental protein 14 binds to the serum transporter alpha-2 macroglobulin. Submitted, 2001.

[Over 10 additional manuscripts in preparation.]

Abstracts:

Weber, M.C. and **Tykocinski, M.L.** Use of episomal vectors for antisense RNA-mediated inhibition of ICAM-1 in human bone marrow stromal cells. J. Cell. Biochem. Suppl. 17E:199, 1993.

Fayen, J., Huang, J.H., Meyerson, H., Zhang, D., Getty, R., Chu, R., Kaplan, D., Greenspan, N., and **Tykocinski, M.L.** Soluble human CD8 binds to a recombinant fusion protein which incorporates the class I MHC alpha3 domain. AAI, Denver, CO, 21-25 May 1993. 288A:1647.

Feng, Y., Morrow, D.M., and **Tykocinski, M.L.** A novel hematopoietic isoform of placental protein 14 (PP14). AAI, Denver, CO; 21-25 May 1993. J. Immunol. 203A:1155

Srisuchart, B., LaCell, K.A., **Tykocinski, M.L.**, Kaplan, D.R. CD8-dependent immunoregulation in a murine in vivo model. AAI, Denver, CO; 21-25 May 1993. 280A:1602.

Tsao, H.M., Kaplan, D., and **Tykocinski, M.L.** Molecular dissection of the human CD8 molecule. AAI, Denver, CO; 21-25 May, 1993. 288A:1649.

Meyerson, H., Fayen, J. Kaplan, D., and **Tykocinski, M.L.** The immunoglobulin light chain variable (Ig-V) homology domain of CD8 can mediate binding to class I MHC molecules. AAI, Denver, CO; 21-25 May 1993. 288A:1648

Singh, N., Zoeller, R.A., **Tykocinski, M.L.**, Lazarow, P.B. and Tartakoff, A.M. The addition of lipid substituents of mammalian protein glycosyl phosphoinositol anchors. American Society for Cell Biology 3rd annual meeting, New Orleans, December, 1993.

Trojan, J., Johnson, T.R., Rudin, S.D., Blossey, B.K., Shevelev, A., Abdul-Karim, F.W., Anthony, D.D., **Tykocinski, M.L.**, Ilan, Ju., and Ilan, Jo. Gene therapy of murine teratocarcinoma, American Association for Cancer Research, Inc., January, 1994.

Brunschwig, E. and **Tykocinski, M**. Glycosyl-phosphatidylinositol-modified murine B7-1 retains costimulatory activity. Experimental Biology '95, Atlanta, GA, April, 1995.

Meyerson, H., Huang, J.-H, Fayen, J., Getty, R., Greenspan, N., and **Tykocinski, M.** Functional dissociation of CD8 's immunoglobulin homologue and connecting peptide domains. Experimental Biology '95, Atlanta, GA, April, 1995.

Fayen, J. and **Tykocinski, M.** Purification of a glycosylphosphatidylinositol-modified form of human CD8 incorporating a polyhistidine tag. Experimental Biology '95, April, 1995.

Fayen, J. Chen, A. and **Tykocinski, M.** Polyhistidine-tagging of glycosyl-phosphatidylinositol-modified costimulators. AACR, New Orleans, LA, 1996.

Chen, A., Meyerson, H., and **Tykocinski, M**. Glycosylation is not required for B7-1 (CD80) association with its counter-receptors. AAI97, February, 1997.

Riely, G.J., Koo, P.H., and **Tykocinski, M.L.** Interaction of placental protein 14 with α_2-macroglobulin. AAI, San Francisco, 1998.

Weber, M.C., and **Tykocinski, M.L.** Cloning and expression profiling of murine clk2 mRNA. AAI, San Francisco, 1998.

Fayen, J., Huang, J.-H., and **Tykocinski, M.L.** Anti-MHC class II monoclonal antibodies inhibit the stimulation of $\gamma\delta$ T cells by Daudi cells. AAI, San Francisco, 1998.

Kopf, E., Bibi, O., Ayeah, S., **Tykocinski, M.L.**, Vitner, K., Locijenga, L.H.J., deGroot, N., Hochberg, A. *The effect of retinoic acid on the activation of the human H19 promoter by a 3' downstream region.* FEBS Letters 432(3) August,1998.

Editorials, Reviews, Chapters:

Medof, M.E. and **Tykocinski, M.L.** The cytoplasmic extension as a determinant for glycoinositolphospholipid anchor substitution. *In* Glycobiology, Welply, J.K. and Jaworski, E.
(eds.) Wiley-Liss, Inc., New York, pp. 17-22, 1990.

Tykocinski, M.L., Hambor, J.E., Weber, M.C., Groger, R.K. and Kaplan, D.R. Antisense RNA analysis in lymphocytes: defining new functions for cell surface molecules (review article). *In* Advances in Gene Technology: The molecular biology of immune diseases and the immune response. Streilein, J.W., *et al.* (eds.), Oxford Univ. Press, ICSU Short Reports 10:128-129, 1990.

Tykocinski, M.L., and Kaplan, D.R. A multifunctional perspective of the CD8 molecule. *In* NK Cell Mediated Cytoxicity: Receptors, signaling and mechanisms. Lotzova, E., and Herberman, R.B. (eds.), Ann Arbor: CRC Press, pp. 393-408,1992.

Johnson, T.R., Trojan, J., Rudin, S.D., Ilan, Ju., **Tykocinski, M.L.**, and Ilan, J. Evoking an immune response to glioblastoma cells transfected with episome-based plasmid expressing antisense transcripts to insulin-like growth factor I. Molecular Genetics of Nervous System Tumors, Chapter 35, pp. 387-400, 1993 Wiley-Liss, Inc.

Tykocinski, M. L., Na Xiong, Dwight M. Morrow. Platelet Immunoregulatory Factors, in Stem Cells: Thrombopoietin and Cytokine Regulation of Patelet Production, AlphaMed Press, Volume 14, Supplement 1, pp. 240-245, 1996.

Tykocinski, M.L. Engineering cellular cancer vaccines: gene and protein transfer options, in Gene Therapy of Cancer, eds. Gerson, S., and Lattime, E., Academic Press, Chapter19, pp.301-318, 1998.

EXHIBIT E

PROFESSIONAL ACTIVITIES

Executive Training Programs:

1999	Program for Chiefs of Clinical Services, Harvard School of Public Health (Boston, MA)
1999	Executive Development Seminar, AAMC Management Education Programs (Ft. Lauderdale, FL)

Editorial Positions:

1989 -	Ad Hoc reviewer for Am. J. Pathol. J. Immunol. Methods, J. Virology J. Immunology, Cancer Res., Immunity, Annals of Neurology, Blood, J. Clinical Invest., Am. J. of Surg. Pathol.
1996 -	Editorial Board, American Journal of Pathology

Academic Committees:

Case Western Reserve University:

1984-90	Codirector, Immunology Research Seminar Series (University Hospitals of Cleveland, sponsored by Dept. of Pathology)
1985-98	Faculty Member, Medical Sciences Training Program, CWRU, NIH-funded
1988	Member, Search Committee for Director of Division of Human Genetics, CWRU
1988-91	At-large preclinical representative, Faculty Council, CWRU
1989-90	Member, Search Advisory Committee for Dean of Medicine and Vice-President for Medical Affairs, CWRU
1988-95	Codirector, Immunology Seminar Series, CWRU
1990-95	Member, Research Committee, CWRU School of Medicine
1990-91	Member, Steering Committee, Faculty Council, CWRU School of Medicine
1990-95	Member, Department of Pathology Committee on Appointment Promotion and Tenure, CWRU
1991-95	Chairman, Department of Pathology Committee on Appointments, Promotion and Tenure, CWRU
1991	Judge, PEW Scholars Program in Biomedical Sciences
1991-94	Senator, University Faculty Senate, CWRU
1991-98	Member, Executive Council, CWRU Cancer Center
1993-94	Member, Pathology Faculty Search Committee, CWRU
1994-95	Member, CWRU School of Medicine Conflict of Interest Committee
1996-98	Member, CWRU School of Medicine Technology Transfer Committee
1997-98	Member, Outreach Seminar Program, CWRU

1998 Member, Nominating Committee, School of Medicine, CWRU
1998 Member, Millenium Research Planning Committee (appointed by Dean), CWRU School of Medicine
1998 Member, Search Committee for Chairperson, Department of Biochemistry, CWRU

University of Pennsylvania Health System:

1998-99 Member, Clinical Practice Executive Committee (CPEC)
1998-99 Member, Steering Committee of the Standing Committee of Department Chairs (appointed by Dean/CEO)
1998 - Member, Administrative Forum
1998 - Member, CPEC Finance Subcommittee
1998 - Member, Clinical Chairs and Chiefs Advisory Committee
1998 - Member, Medical Board
1998 - 2000 Member, Enterprise Master Patient Index Steering Committee
1998 - Member, Standing Committee of Department Chairs
1998 - Member, Basic Science Chairs
1998 - 2000 Member, Information Management Planning Council
1999 - Member, Clinical Practices of the University of Pennsylvania (CPUP) Board of Directors (formerly CPEC)
1999 - Member, Executive Committee, CPUP
1999 - 2000 Member, Hunter Group Physicians Advisory Work Group
1999 - Member, Academic Review Committee (appointed by Dean/CEO)
1999 - Member, Cancer Center Translational Research Committee
2000 Member, Arthur Andersen Consultation Committee (appointed by Dean/CEO)
2000 - Member, Steering Committee of the Standing Committee of Department Chairs (appointed by Dean/CEO)
2000 - Chair, Basic Science Chairs

University of Pennsylvania Department of Pathology and Laboratory Medicine:

1998 - Member, Committee on Appointments and Promotions
1998 - Chair, Executive Committee
1998 - Chair, Section Chiefs Committee

Major Teaching and Clinical Responsibilities:

Case Western Reserve University:

1985-98 Lecturer, Biological Basis of Diseases (first-year medical students), CWRU School of Medicine
1985-90 Subject Committee Chairman, Immunology Component of Biological Basis of Disease I, CWRU School of Medicine
1985-90 Member, Review Committee for interim and comprehensive examinations in Biological Basis of Disease 1, CWRU

1985-98	Course Organizer and Lecturer, Advanced Molecular Immunology (graduate level course), CWRU
1985-98	Lecturer, Advanced Immunobiology (graduate level course), CWRU
1985-98	Lecturer, Immunology of Infectious Disease (graduate level course), CWRU
1986-98	Lecturer, Fundamental Immunology, (undergraduate level course), CWRU
1986-98	Lecturer, Imunopathology, (graduate level course), CWRU
1986-96	Lecturer, "Molecular Biology in medicine," (for incoming Pediatric Fellows), University Hospitals of Cleveland
1990-98	Guest lecturer (annual) immunology course, Northeastern Ohio Universities College of Medicine, Rootstown, OH

University of Pennsylvania:

1998-	Director, Clinical Laboratories of the Department of Pathology and Laboratory Medicine

Advisory Boards:

1999-	Scientific Advisory Board A.J. Renner & Associates Biotechnology Advantage Program (Illinois)

Lectures by Invitation:

Spring 1983	Plenary Speaker, International Workshop on Major Histocompatibility Genes (Airlie House, VA)
Spring 1985	Invited Speaker, Research Seminar Series at the Cleveland Clinic (Cleveland, OH)
Fall 1986	Invited Speaker, MIT Workshop on "Complement genes" (Boston, MA)
Fall 1987	Plenary Speaker, EMBO Workshop on "Post-translational Modification of Proteins by Lipids" (Les Diablerets, Switzerland)
Winter 1988	Invited Speaker, Research Seminar Series at Rockefeller University (New York, NY)
Winter 1988	Invited Speaker, NIH Immunology Research Seminar Series (Bethesda, MD)
Spring 1988	Invited Speaker, American Association of Cancer Research minisymposium on "Regulation of Gene Expression" (New Orleans, LA)
Fall 1988	Molecular Biology Seminar Series at Roswell Park Memorial Institute (Buffalo, NY)
Winter 1989	Plenary Speaker, UCLA Symposium on "Glycobiology" (Frisco, CO)

Spring 1989	Invited Speaker, Immunology Seminar Series at Cleveland Metropolitan General Hospital (Cleveland, OH)
Summer 1989	Invited Speaker, 7th International Congress of Immunology - Workshop on "Genes for Accessory Molecules of the T Cell Receptor" (Berlin, W. Germany)
Fall 1989	Invited Speaker, Pathology Seminar Series at New York University School of Medicine (New York, NY)
Fall 1989	Invited Speaker, Immunology Seminar Series at Stanford Medical School (Palo Alto, CA)
Fall 1989	Invited Speaker, Research Seminar Series at University of Cincinnati Medical Center (Cincinnati, OH)
Winter 1990	Plenary Speaker, Miami Bio/Technology Winter Symposium on "Advances in Gene Technology: Molecular Basis of Immune Diseases" (Miami, FL)
Winter 1990	Plenary Speaker, UCLA Symposium on "Synthetic Peptides: Approaches to Biological Problems" (Frisco, CO)
Summer 1990	Plenary Speaker, 4th International Cell-Mediated Cytotoxicity Workshop (Oglebay Park, W. VA)
Fall 1990	Invited Speaker, Seminars in Cell Pathology at Cornell University (Ithaca, NY)
Fall 1990	Invited Speaker, Immunology Seminar Series at Mount Sinai School of Medicine (New York, NY)
Winter 1991	Invited Speaker, NIH Pathology B Study Section Workshop (Tamarron, CO) (Meeting Report in Cancer Research 51:5440-5444, 1991)
Spring 1991	Invited Speaker, 5th Annual Meeting of the CWRU Cancer Center; title: on "Gene Transfer and Therapy" (Cleveland, OH)
Spring 1991	Invited Speaker, Biochemistry Seminar Series at Hebrew University (Jerusalem, Israel)
Fall 1991	Invited Speaker, Special Research Seminar at the Center for Molecular Genetics, University of California - San Diego (San Diego, CA)
Fall 1991	Plenary lecture, Annual meeting of the Meridia-Suburban Medical Society (Cleveland, OH)

Fall 1991	Invited Speaker, Immunology Seminar Series at Memorial Sloan-Kettering (New York, NY)
Fall 1991	Invited Speaker, Immunology Seminar Series at University of California--San Francisco (San Francisco, CA)
Fall 1991	Invited Speaker, Biochemistry Seminar Series at CWRU (Cleveland, OH)
Fall 1991	Invited Speaker, Research Seminar Series at the Cleveland Clinic (Cleveland, OH)
Spring 1992	Invited Speaker, Immunology Seminar Series at University of Washington (Seattle, WA)
Spring 1992	Plenary Speaker, International Congress on "Molecular Approaches to Nephrology: Prospects in Diagnosis and Management"; Chair of round table on "Molecular Aspects of Renal Transplantation" (Bari, Italy)
Spring 1992	Invited Speaker, Immunology Seminar Series at the Cleveland Clinic (Cleveland, OH)
Fall 1992	Invited Speaker, Seminar Series in the Pharmacological Sciences, CWRU (Cleveland, OH)
Fall 1992	Invited Speaker, Pathology Research Seminar at the University of Washington (Seattle WA)
Fall 1992	Invited Speaker, Research Seminar at Brown University (Providence, RI)
Fall 1992	Plenary Speaker, 45th Annual Symposium on Fundamental Cancer Research entitled "Immunobiology of Cancer: Cellular and Molecular Mechanisms" (Houston, TX)
Winter 1993	Invited Speaker, Research Seminar at Northeastern Ohio Universities College of Medicine, Department of Microbiology and Immunology (Rootstown, OH)
Spring 1993	Invited Speaker, Immunobiology Seminar Series at Yale University (New Haven, CT)
Spring 1993	Invited Guest of People's Republic of China; 14-day lecture tour in three Chinese cities (Shanghai, Xi'an, and Beijing)
Summer 1993	Plenary Speaker, International Symposium on "Tumors of the Central Nervous System" (Milan, Italy)
Fall 1993	Invited Speaker and consultant, Agracetus, Inc. (Madison, WI)

Winter 1994	Cleveland Cancer Group, Cleveland Clinic (Cleveland, OH)
Winter 1994	Skin Diseases Research Center (Cleveland, OH)
Winter 1994	Biochemistry Seminar Series (Cleveland, OH)
Spring 1994	Visiting Scientist, Department of Biochemistry, Hebrew University (Jerusalem, Israel)
Summer 1994	Plenary Speaker, Biotech 94 Conference, sponsored by the State of Ohio's Edison Biotechnology Center (Columbus, OH)
Winter 1995	Co-chairperson, Mini-Symposium entitled "Lessons from Hematopoietic Malignancies" at the Sixth International Workshop on Chromosomes in Solid Tumors, Feb. 19-21, 1995 (Tucson, AZ)
Spring 1995	Co-chairperson, Poster Discussion Session entitled "Gene Therapy I" at the 86th Annual Meeting of the American Association of Cancer Research, March 18-22, 1995 (Toronto, Canada)
Spring 1995	Plenary Speaker, Mini-symposium on Antisense Gene Therapy, ECOG (Eastern Cooperative Oncology Group) meeting (Denver, CO)
Spring 1995	Plenary Speaker, Warner-Lambert/Parke-Davis Award lecture, Experimental Biology '95 Meeting (Atlanta, GA)
Summer 1995	Invited Speaker, Special course entitled "Transgenic Animals to Model Human Diseases of the Nervous System" at the Annual Meeting of the American Association of Neuropathologists, June 7, 1995 (San Antonio, TX)
Fall 1995	Plenary Speaker, Symposium entitled "Gene Therapy for Immune Deficiencies and Cancer" to commemorate the 5th anniversary of the first human gene therapy clinical trial (Cleveland, OH)
Fall 1995	Research Seminar at Mayo Clinic (Jacksonville, FL)
Fall 1995	Pathology Seminar at Emory University (Atlanta, GA)
Fall 1995	Plenary Speaker, Amici Medicinae program entitled: "Genes: New Weapons to Fight Cancer and Arteriosclerosis" (Cleveland, OH)
Winter 1996	Plenary Speaker, Keystone Symposium on Molecular and Cellular Biology entitled "Molecular Regulation of Platelet Production" (Taos, NM)

Winter 1996	Plenary Speaker, Keystone Symposium on Molecular and Cellular Biology entitled "Exploring and Exploiting Antibody and Ig Superfamily Combining Sites" (Taos, NM)
Spring 1996	Cancer Research Seminar, Karmanos Cancer Institute, Wayne State University (Detroit, MI)
Spring 1996	Immunology Seminar Series at Johns Hopkins, University (Baltimore, MD)
Spring 1996	Co-chairperson, Poster Discussion Session entitled "Developing Effective Gene Therapy: Promising Strategies and Vectors" at the 87th Annual Meeting of the American Association of Cancer Research, April 20-24, 1996 (Washington, DC)
Spring 1996	Plenary Speaker, The 13th International Hammersmith Conference, May 27-30, 1996 (Crete, Greece)
Summer 1996	Research Seminar at Tulane Medical School (New Orleans, LA)
Winter 1997	Rammelkamp Research Seminar, MetroHealth Medical Center (Cleveland, OH)
Winter 1997	Co-Chairperson, Poster Discussion Session, Keystone Symposium on Molecular and Cellular Biology entitled "Cellular Immunology and the Immunotherapy of Cancer-III" (Copper Mountain, CO)
Winter 1997	Research Seminar at the Institute of Human Genetics, University of Minnesota (Minneapolis, MN)
Spring 1997	Research Seminar at the Public Health Research Institute (New York, NY)
Spring 1997	Immunology Seminar Series at CWRU (Cleveland, OH)
Fall 1997	Plenary Speaker, Meeting on "Regulation of Cell Growth and Cell Death" held at Mohican State Park Conference Center, Sept. 24-25, 1997 (Perrysville, OH)
Fall 1997	Plenary Speaker, International Meeting on "Interaction of GPI anchors with Biological Membranes," Sept. 14-17, 1997 (Splugen, Switzerland)
Fall 1997	Plenary Speaker, President's Weekend for Leading CWRU Alumni (Cleveland, OH)
Fall 1997	Pathology Research Seminar at University of Pennsylvania (Philadelphia, PA)

Winter 1998	City-Wide GI Grand Rounds entitled "Frontiers in Gastroenterology and Hepatology" (Cleveland, OH)
Spring 1998	Plenary Speaker, Molecular Virology Program Retreat on "Gene Therapy Initiatives," Ireland Cancer Center (Cleveland, OH)
Fall 1998	Featured Speaker, Biomedical Graduate Studies Convocation, University of Pennsylvania (Philadelphia, PA)
Fall 1998	Melanoma Group Seminar, Wistar Institute (Philadelphia, PA)
Fall 1998	Plenary Speaker, Institute for Human Gene Therapy 6th Annual Retreat, University of Pennsylvania (Absecon, NJ)
Winter 1999	Physician Scholar Seminar Series, "The Altered Immunological State of Pregnancy: From Clinical Observations to Protein Pharmaceuticals" University of Pennsylvania (Philadelphia, PA)
Winter 1999	Research Seminar at Institute for Medicine and Engineering Seminar Series, University of Pennsylvania (Philadelphia, PA)
Winter 1999	Pathology Grand Rounds, Hospital of the University of Pennsylvania (Philadelphia, PA)
Summer 1999	Plenary Speaker, Association of Pathology Chairs, PRODS Meeting, Session on "Research by Residents: Issues of Funding and Organization" (Boulder, CO)
Fall 1999	Duhring Lecture Series, Department of Dermatology, Hospital of the University of Pennsylvania (Philadelphia, PA)
Fall 1999	Keynote Speaker, Third Joint International Cancer Conference (Capri, Italy)
Fall 1999	Mount Sinai-NYU, Medical Center and Health System, Tisch Hospital Grand Rounds, (New York, NY)
Fall 1999	New York University Medical Center, School of Medicine, Pathology Grand Rounds (New York, NY)
Winter 2000	Quest Distinguished Visiting Professor of Pathology, and Pathology Grand Rounds, John Hopkins University School of Medicine (Baltimore, MD)
Spring 2000	Plenary speaker, Annual Meeting of the Pennsylvania Association of Pathologists: "Pathology in the Millennium: Our past, our future!" (Valley Forge, PA)

Spring 2000	Plenary speaker, Gene Therapy Workshop, Hadassah Florida Central Region Spring Conference (Orlando, FL)
Spring 2000	Plenary speaker, Pennsylvania Association of Pathologists Annual Meeting, May 6-7, 2000 (Valley Forge, PA)
Spring 2000	Co-Chair, Block Symposium on "Immune-based Therapy in Cancer," AAI/CIS Joint Annual Meeting, *Immunology 2000* (Seattle, WA)
Summer 2000	APC/PRODS Annual Meeting wit Pathology Department Administrators, Ivory Tower, Inc. "Leader Breakout Session on Research--Mixing Fun and Profit" (Boulder, CO)
Summer 2000	University of Pittsburgh, Department of Pathology Seminar (Pittsburgh, PA)
Winter 2001	Pluto Society - American Association of University Pathologists (Maui, HI)

Organizing Roles in Scientific Meetings:

1992	Organizer, First Annual Immunology Research Workshop, Institute of Pathology, CWRU, held at Gwinn Estate
1992	Member, Program Planning Committee for the 6th Annual Retreat of The CWRU Cancer Research Center, "Developments in Molecular and Clinical Neuro-oncology"

Patents:

Tykocinski, Mark L.: Method of reducing cellular immune responses involving T-cells using CD8-bearing antigen presenting cells. U.S. Patent Number 5,242,687, 1993

Tykocinski, Mark L.: CD8 derivatives and methods of use for cellular modulation and enhancements of cellular engraftment. U.S. Patent Number 5,601,828, 1997.

Six U.S. patent applications pending with over twenty other associated continuances-in-part and foreign patent filings (relating to therapies for cancer, alloimmune and autoimmune diseases, and acute inflammatory conditions).